215. *The Chemistry of Simple Heterocyclic Systems. Part II. Condensations of* 4-*Chloro*-6- *and* 4-*Chloro*-7-*nitroquinazoline with Amines.*

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The condensation of 4-chloro-6- and -7-nitroquinazoline with a variety of primary aromatic and heterocyclic amines has been studied, and the results have been correlated with the basic strengths and nature of the amines. It has been established (i) that the chloro-compounds do not condense with primary heterocylic amines in which a prototropic change to an imino-dihydro-derivative is formally possible, and (ii) that condensation occurs between the chloro-compounds and aromatic amines or *Bz*-heterocylic amines provided that the pK_a values of such amines lie within the approximate range 1·0—5·2. Condensation does not occur if the pK_a values of the amines lie on either side of this range, and it is concluded that these results accord with the view that the reaction between chloro-heterocylic compounds and amines is acid-catalysed.

During a study of the reactions of 6- and 7-nitro-4-hydroxyquinazoline and their derivatives (Morley and Simpson, *J.*, 1948, 2024), we observed that 4-chloro-6- and -7-nitroquinazoline readily condense with aniline in faintly acid aqueous medium, these conditions being chosen as they had previously been found to be well suited for the production of arylamino-heterocyclic derivatives (cf. Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127, 1131; Banks, Gruhzit, Tillitson, and Controulis, *ibid.*, 1944, **66**, 1771; Andres and Hamilton, *ibid.*, 1945, **67**, 946; Tomisek and Christensen, *ibid.*, 1945, **67**, 2112; Banks and Controulis, *ibid.*, 1946, **68**, 944; Curd and Rose, *J.*, 1946, **343**; Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370). Subsequently it was found that, if 2 : 4-dinitroaniline be substituted for aniline, no reaction occurs, apart from hydrolysis of the chloro- to the hydroxy-quinazolines. This lack of reaction between a weak base and the chloronitroquinazolines seemed of particular interest inasmuch as failures have also been reported for the much more strongly basic dialkylaminoalkylamines (Banks, *loc. cit.*; Curd and Rose, *loc. cit.*), in contrast with the rapid reactions, already referred to, which occur between chloroheterocyclic compounds and amines of intermediate basicity (aniline, *p*-chloroaniline, etc.). Accordingly we have studied the reactivity, in slightly acid aqueous acetone, between 4-chloro-6- and -7-nitroquinazoline and a representative range of amines. In addition to the failure with 2 : 4-dinitroaniline, negative results were also obtained with 1-nitro-2-naphthylamine, benzylamine, 4-amino- and 6-nitro-4-amino-quinoline, 4-amino-, 6-chloro-4-amino-, and 6-nitro-4-amino-cinnoline, 6-nitro-4-aminoquinazoline, and 2-amino-pyridine; in nearly all these cases the non-occurrence of condensation was demonstrated by the isolation of the chloro- or hydroxy-quinazoline, and sometimes by that of the amine also. On the other hand, reaction occurred rapidly between the chloro-compounds and (in addition to aniline) *m*- and *p*-nitroaniline, *p*-anisidine, diaminouracil, 5- and 6-aminoquinoline, and 3-amino-6-methylquinoline, leading to the formation of 6- and 7-*nitro*-4-m- and -p-*nitroanilino*-, -4-p-*anisidino*-, -4-(4′-*amino*-2′ : 6′-*dihydroxy*-5′-*pyrimidylamino*)-, -4-5′- and -4-6′-*quinolylamino*-, and -4-6′-*methyl*-3′-*quinolylamino*-*quinazoline*.

Comparison of these results with published data revealed that the group of non-reacting amines contained bases both stronger and weaker than those which react; *e.g.*, 4-aminoquinoline (does not condense), pK_a 8·46 (Albert and Goldacre, *Nature*, 1944, **153**, 467); aniline (condenses) pK_a 4·7 (Waters, "Physical Aspects of Organic Chemistry," Routledge, 1937, p. 208; Handbook of Chemistry and Physics, Chemical Rubber Publishing Co., 1944); 2 : 4-dinitro-aniline (does not condense), pK_a −4·38 (Glasstone, "Introduction to Electrochemistry," New York, 1942).

In order to throw further light on the possible relations between the basicity of an amine and its ability to react with the chloronitroquinazolines under the particular conditions used, we have determined, as indicated in Table I, the pK_a values of the bases studied in this investigation, in cases where these were lacking. In this table the bases are listed in decreasing order of basic strength, with the proviso that the "second pK_a" value (pK_{a_2}), if shown, takes precedence over the "first pK_a" value (pK_{a_1}) in determining the order of placing; they are also divided into reactive and unreactive groups. The positions of 1-nitro-2-naphthylamine in the Table is uncertain, as, owing to its weak basicity, it was not possible to determine its pK_a value even approximately under the conditions used.

The significance of the "second pK_a" values calls for some explanation. In the case of diaminouracil the determination was made by acid titration of the sulphate (B_2,H_2SO_4; Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667) and is therefore probably an estimation of pK_{a_2}, which, for reasons of the kind discussed by Albert and Goldacre (*loc. cit.*), may be

considered to be that of the " aromatic " amino-group of this compound. With 5- and 6-aminoquinoline, potentiometric titrations were made on the free bases, and thus gave pK_{a_1} values. The question therefore arose as to whether these values are related to the ring-nitrogen or to the

TABLE I.

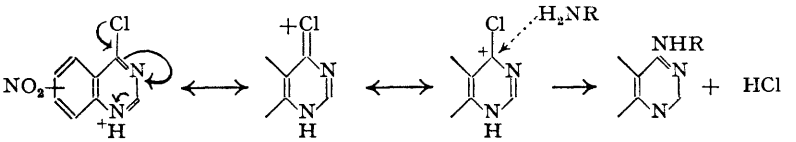
Non-reactive amines.	Solvent.*	Temp.	Ref.	pK_{a_1}.	pK_{a_2}.	Reactive amines.
			4	9·4	—	—
Benzylamine	A	24—25°	1	8·9	—	—
	B	24—25	1	9·2	—	—
4-Aminoquinoline	A	24—25	1, 2	8·45	—	—
2-Aminopyridine	—	—	3	6·85	—	—
			2	7·15	—	—
6-Nitro-4-aminoquinoline ...	A	24—25	1	6·4	—	—
4-Aminocinnoline	A	24—25	1	6·25	—	—
6-Chloro-4-aminocinnoline	A	28	1	5·4	—	—
			4	5·15	—	*p*-Anisidine
6-Nitro-4-aminocinnoline ...	A	24—25	1	5·1	—	—
			5	4·7	—	Aniline
	[A	24—25	1	4·25	—	† 3-Amino-6-methylquinoline]
6-Nitro-4-aminoquinazoline	A	24—25	1	3·7	—	—
			6	2·6	—	*m*-Nitroaniline
	A	24—25	1	—	1·7	Diaminouracil
			2	5·6	1·60 ‡	6-Aminoquinoline
			7	1·1	—	*p*-Nitroaniline
			2	5·5	0·96 ‡	5-Aminoquinoline
[1-Nitro-2-naphthylamine]						
2 : 4-Dinitroaniline	—	—	7	−4·38	—	—

* A = 50% aqueous alcohol. B = water.
† Morley and Simpson, *J.*, 1948, 2024.
‡ Spectrographic determination at 20°; private communication from Professor R. A. Morton.

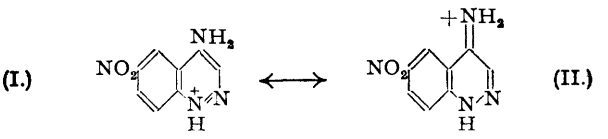
1. This paper. 2. Albert and Goldacre (*loc. cit.*) (in water at 20°). 3. Tropsch, *Monatsh.*, 1914, **35**, 775. 4. Heilbron's " Dictionary of Organic Compounds " (1st Edition). 5. Mean values from Heilbron, Waters, and " Handbook of Chemistry and Physics " (*opp. cit.*). 6. Mean values from Heilbron and Waters (*opp. cit.*). 7. Glasstone, " Introduction to Electrochemistry," New York, 1942.

primary amino-group. From a spectrographic study of the aminoacridines, Craig and Short (*J.*, 1945, 419) concluded that the formation of salts of these bases involves the addition of the first proton to the ring-nitrogen, and Irvin and Irvin (*J. Amer. Chem. Soc.*, 1947, **69**, 1091) state that this is probably true also of various 4-aminoquinolines. Professor R. A. Morton has kindly investigated the absorption spectra of 5- and 6-aminoquinoline in acid solution, and has informed us that, in these compounds also, the first proton is in all probability accepted by the ring-nitrogen. The basicities of the amino-groups of these compounds are therefore indicated by the pK_{a_2} values, which were calculated from the spectrographic data. (3-Amino-6-methylquinoline was not examined spectrographically, and its exact position in the Table is therefore uncertain, but a similar state of affairs no doubt holds good also in this case).

It will be seen from Table I that the pK_a values of amines which react with the chloronitroquinazolines fall within a limited range (in the definition of which pKa_2 again takes precedence over pK_{a_1}), the extreme values of the examples studied being 5·15 and 0·96, and that the reaction does not occur with amines of which the pK_a values lie on either side of this range. This is precisely the behaviour which would be expected if, as suggested by Banks, by Andres and Hamilton, and by Banks and Controulis (*locc. cit.*), the reaction between amines and chloro-heterocyclic compounds is acid-catalysed; for, according to the amount by which the basicity of the primary amine exceeds that of the heterocyclic chloro-compound, the share of the available protons acquired by the latter will be correspondingly smaller and the condensation consequently inhibited (Case A); on the other hand, a reduction in basicity of the primary amine will diminish proportionately its power of co-ordination with the kationoid C_4 (see below), and ultimately a point will be reached beyond which the anionoid attack on the chloro-heterocyclic compound is no longer possible (Case B).



Further reference to Table I shows that in no case does a compound containing a "heterocyclic" amino-group (*i.e.*, an amino-group attached to C_2 or C_4 of the heterocyclic ring) react with the chloro-compounds, even if the pK_{a_1} value of the amino-compound falls within the "active" range, as with 6-nitro-4-amino-cinnoline and -quinazoline. This lack of reactivity is without doubt due to the fact that the monokations are greatly stabilised by resonance [*e.g.*, forms (I) and (II) for 6-nitro-4-aminocinnoline] of the type discussed for 4-aminoquinoline



by Albert and Goldacre (*loc. cit.*), and pK_{a_1} for such compounds therefore falls below the lower critical limit (Case B). In the case of 4-amino-heterocyclic compounds of high pK_{a_1} values, the conditions of Case A could also operate.

After this work was completed, a note by Meyer and Bouchet (*Compt. rend.*, 1947, **225**, 63) appeared, in which the condensation of 4-chloroquinaldine with various amines (usually in acetic acid–sodium acetate) was described. Their results, although only of a qualitative character, are in general agreement with our own; thus these authors conclude that the reaction depends on the basicity of the amine used, and that it is successful with diazotisable amines, but fails with tautomerisable amino-heterocyclic compounds.

Experimental.

Melting points are uncorrected.

The experiments shown in Table II were carried out by heating under reflux for ½ hour a mixture of 4-chloro-6- or -7-nitroquinazoline (usually 0·4 g.) and the appropriate amine (5—10% excess) in 50% aqueous acetone (usually 20 c.c.) containing 2—3 drops of concentrated hydrochloric acid. It was

Table II.

		Products isolated from attempted condensation with 4-chloro-6-nitro-quinazoline.			Products isolated from attempted condensation with 4-chloro-7-nitro-quinazoline.		
Expt. no.	Amine.	Chloro-quinazo-line.	Hydroxy-quinazo-line.	Amine.	Chloro-quinazo-line.	Hydroxy-quinazo-line.	Amine.
1.	2 : 4-Dinitroaniline	−	+	+	−	+	+
2.	1-Nitro-2-naphthylamine	−	+	+	−	+	+
3.	6-Nitro-4-aminoquinazoline [1]	−	+	+	−	+	+
4.	6-Chloro-4-aminocinnoline [2]	−	+	+	−	+	+
5.	6-Nitro-4-aminoquinoline [3]	−	+	+	−	+	+
6.	4-Aminocinnoline [2,4]	−	+	+	−	+	+
7.	Benzylamine [4]	−	+		+	−	
8.	4-Aminoquinoline	+	−	+	+	−	+
9.	2-Aminopyridine	+	−		+	−	
10.	6-Nitro-4-amino-cinnoline [2]			+			+

[1] Morley and Simpson, *J.*, 1948, 360.
[2] Keneford, Schofield, and Simpson, *J.*, 1948, 358.
[3] Simpson and Wright, *J.*, 1948, 1707.
[4] In these experiments complete separation and identification of the total reaction product was not achieved. A blank space in the Table indicates that no search was made for the compound in question.

observed that the pH of the reaction medium was *ca.* 7 in those experiments in which the chloro-compounds were recovered; if the pH was appreciably (*ca.* 1 unit or more) on either side of the neutral point, hydrolysis of the chloro- to the hydroxy-quinazoline resulted. The chloroquinazolines separated directly from the hot solution after removal of acetone, and the hydroxyquinazolines and amines were isolated by utilising their respective solubilities in alkali and acid; the yields of products were *ca.* 80—90%.

Preparation of 6- *and* 7-*Nitro*-4-*arylaminoquinazolines.*—The following compounds were prepared from the appropriate chloroquinazoline and amine under the conditions used for the experiments listed above; at the end of each reaction (½ hour under reflux) the suspension was basified with ammonia, and the resultant amines were recrystallised from suitable solvents (referred to numerically below) as follow: (1) acetic acid; (2) aqueous acetic acid; (3) aqueous pyridine; (4) aqueous alcohol; (5) absolute alcohol. 6-*Nitro*-4-m-*nitroanilinoquinazoline* formed brittle, yellow prismatic needles (yield, 85%) (1), m. p. 270—271° (Found: C, 53·75; H, 3·1; N, 22·1. $C_{14}H_9O_4N_5$ requires C, 54·0; H, 2·9; N, 22·5%). The 7-*nitro*-isomer, clusters of pale yellow soft needles (1), had m. p. 284—285° (yield, 83%) (Found: C,

52·6; H, 3·1; N, 22·2. $C_{14}H_9O_4N_5,\frac{1}{2}H_2O$ requires C, 52·5; H, 3·1; N, 21·9%). 6-*Nitro*-4-p-*nitroanilinoquinazoline*, m. p. 319—320° (decomp.), formed bright yellow, fluffy needles (2) (yield, 98%) (Found: C, 54·4; H, 3·05; N, 22·8. $C_{14}H_9O_4N_5$ requires C, 54·0; H, 2·9; N, 22·5%). The 7-*nitro*-isomer separated (1 or 2) in stout, yellow, brittle needles, m. p. 291—292° (decomp.) (yield, 95%) (Found: C, 53·9; H, 3·0; N, 22·3%). 6-*Nitro*-4-6′-*methyl*-3′-*quinolylaminoquinazoline* crystallised (1) in warts of fine, deep yellow needles, m. p. 294—295° (yield, 100%) (Found: C, 65·8; H, 3·9; N, 20·8. $C_{18}H_{12}O_2N_5$ requires C, 65·25; H, 3·95; N, 21·1%). The 7-*nitro*-isomer (yield, 100%), m. p. 337—338° (decomp.), formed bright yellow, feathery needles (1) (Found: C, 64·8; H, 3·8; N, 20·9%). The product from 4-chloro-6-nitroquinazoline and 4 : 5-diamino-2 : 6-dihydroxypyrimidine separated as a pale orange solid when the reaction mixture was brought to pH 7; it did not melt at 340°, and was not purified (yield, 76%). 7-*Nitro*-4-4′-*amino*-2′ : 6′-*dihydroxy*-5′-*pyrimidylaminoquinazoline* was isolated similarly (yield, 81%), and was purified by dissolution in 0·25N-sodium hydroxide, cautious acidification, and recrystallisation (3); it formed orange micro-crystals, which did not melt at 340° (Found: C, 44·3; H, 3·7; N, 29·2. $C_{12}H_9O_4N_7,\frac{1}{2}H_2O$ requires C, 44·4; H, 3·1; N, 30·2%). 6-*Nitro*-4-p-*anisidinoquinazoline* (yield, 100%) crystallised in soft orange needles (4) or dense, bright red prisms (5), m. p. 203—205° (Found: C, 60·5; H, 3·8; N, 19·2. $C_{15}H_{12}O_3N_4$ requires C, 60·8; H, 4·1; N, 18·9%). The 7-*nitro*-isomer (yield, 100%) formed soft maroon needles (5), m. p. 236—238° (Found: C, 60·5; H, 4·1; N, 19·0%). 6-*Nitro*-4-5′-*quinolylaminoquinazoline* (96% yield), m. p. 282—283° (decomp.), formed soft buff-coloured needles (4) (Found: C, 61·2; H, 3·6; N, 20·8. $C_{17}H_{11}O_2N_5,H_2O$ requires C, 60·9; H, 3·9; N, 20·9%). The 7-*nitro*-isomer (95% yield) had m. p. 301—302° (decomp.), and crystallised as yellow needles (2) (Found: C, 63·95; H, 3·5; N, 22·2. $C_{17}H_{11}O_2N_5$ requires C, 64·3; H, 3·5; N, 22·1%). 6-*Nitro*-4-6′-*quinolylaminoquinazoline* (83% yield), clusters of minute yellow needles (1), had m. p. 333—335° (decomp.) (Found: C, 64·2; H, 3·5; N, 22·4. $C_{17}H_{11}O_2N_5$ requires C, 64·3; H, 3·5; N, 22·1%). 7-*Nitro*-4-6′-*quinolylaminoquinazoline dihydrochloride* (yield, 72%) crystallised from N-hydrochloric acid in pale yellow needles, m. p. 319—320° (decomp.) (Found: C, 50·5; H, 3·7; N, 17·0. $C_{17}H_{11}O_2N_5,2HCl,H_2O$ requires C, 50·0; H, 3·7; N, 17·1%).

A characteristic reaction of the arylaminoquinazolines was the production of a deep-red colour on treatment with dilute aqueous–alcoholic alkali.

Determination of pK_a *Values.*—The determinations were carried out by means of a Cambridge portable pH meter, mechanically-stirred solutions of the bases (30—40 mg.) in 50% aqueous alcohol (50 c.c.) being titrated with 0·1N-aqueous hydrochloric acid at 24—25°; the pK_a values were read from the titration curves at half-neutralisation points. For values of 4 and over, the results given in Table I are uncorrected. For values below 4, *i.e.*, where the observed curve gradually approaches the blank (acid dilution) curve as the basicity diminishes, corrected pK_a values were obtained from the equation (Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405)

$$pK_a = pH + \log\frac{c/2 - [H^+]}{c/2 + [H^+]},$$

where c = initial concentration of base, and the values of pH and $[H^+]$ are those at the calculated half-neutralisation point. This equation gives a correction for the error introduced into a straightforward pK_a determination by the hydrolysis of the salt when the base is weak. For a given concentration and below a certain pH value, however, the magnitude of the correction (the second term on the right-hand side) increases very rapidly with small decreases in pH. There is thus a lower critical limit of observed pK_a value (about 2·7 in our experiments) below which the " corrected " values have no real quantitative significance; for this reason the value for diaminouracil sulphate is only very approximate, and no result of any significance could be obtained for 1-nitro-2-naphthylamine.

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